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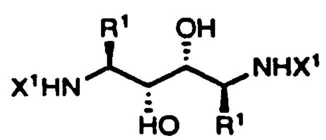
NEW ASPARTIC PROTEASE-INHIBITING 1,4-DIAMINOBUTANE-2,3-DIOLS + ARE USED TO TREAT [illegible] RETROVIRAL INFECTION ESPECIALLY HIV

(54) Title: INHIBITORS OF RETROVIRAL PROTEASES



(I)

(57) Abstract

Compounds useful as inhibitors of retroviral proteases characterized by structure (I), wherein the X^1 groups may consist of 0 to 2 α-amino acid groups terminally substituted by hydrogen or one of a number of end groups, and the R^1 group can be selected from a wide variety of hydrocarbon radicals. Compounds which exhibit a protease activity inhibition constant Ki of less than 50 are desired.

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TITLE

INHIBITORS OF RETROVIRAL PROTEASES

BACKGROUND OF THE INVENTION

This invention relates to compounds which are inhibitors of aspartic proteases, particularly of retroviruses.

Retroviruses, that is, viruses within the family of Retroviridae, are a class of viruses which transport their genetic material as ribonucleic acid rather than deoxyribonucleic acid. Also known as RNA-tumor viruses, their presence has been associated with a wide range of diseases in humans and animals. They are believed to be the causative agents in pathological states associated with infection by Rous sarcoma virus (RSV), murine leukemia virus (MLV), mouse mammary tumor virus (MMTV), feline leukemia virus (FeLV), bovine leukemia virus (BLV), Mason-Pfizer monkey virus (MPMV), simian sarcoma virus (SSV), simian acquired immunodeficiency syndrome (SAIDS), human T-lymphotropic virus (HTLV-I, -II) and human immunodeficiency virus (HIV-1, HIV-2), which is the etiologic agent of AIDS (acquired immunodeficiency syndrome) and AIDS related complexes, and many others. Although the pathogens have, in many of these cases, been isolated, no satisfactory method for treating this type of infection has been developed. Among these viruses, the HTLV and HIV have been especially well characterized.

Critical to the replication of retroviruses is the production of functional viral proteins. Protein synthesis is accomplished by translation of the open reading frames into polyprotein constructs, corresponding to the gag, pol and env reading frames. The gag

and pol precursor proteins, are processed by a viral protease into the functional proteins. The HIV-1 protease has been classified as an aspartic acid protease (Meek et al., Proc. Natl. Acad. Sci. USA, 88, 1841 (1989)). The proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host and is essential to the life cycle of the retrovirus. In fact, it has been demonstrated that retroviruses which lack the protease or contain a mutated form of it, lack infectivity. See Katoh et al., Virology, 145, 280-92(1985), Crawford, et al., J. Virol., 53, 899-907(1985), Debouck, et al., Proc. Natl. Acad. Sci. USA, 84, 8903-6(1987). Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

Methods to express retroviral proteases in E. coli have been disclosed (Debouck, et al., Proc. Natl. Acad. Sci. USA, 8903-06(1987) and Tomasselli et al., Biochemistry, 29, 264-9 (1990) and refs. therein).

Inhibitors of recombinant HIV protease have been reported (Dreyer et al., Proc. Natl. Acad. Sci. USA, 86, 9752-56 (1989); Tomasselli et al. supra; Roberts et al., Science, 248, 358 (1990); Rich et al., J. Med. Chem., 33, 1285-88 (1990); Sigal et al., Eur. Pat. Appl. No. 337 714; Dreyer et al. Eur. Pat. Appl. No. 352 000). Moreover, certain of these inhibitors have been shown to be potent inhibitors of viral proteolytic processing in cultures of HIV-1 infected T-lymphocytes (Meek et al., Nature (London), 343, 90 (1990) and by Roberts et al. supra).

The limitations of current strategies for aspartic protease inhibition include (1) oral bioavailability; (2) plasma clearance lifetimes (e.g., through biliary excretion or degradation); (3) selectivity of inhibition; and (4) in the case of intracellular targets, membrane permeability or cellular uptake. The present invention relates to a new inhibitors of retroviral and aspartic proteases. Unlike previously described inhibitors , the compounds of this invention are not analogues of peptide substrates possessing a scissile dipeptide mimetic. They also deviate substantially from peptide substrate-like structure in that they do not possess a conventional amino-to-carboxyl terminus orientation.

SUMMARY OF THE INVENTION

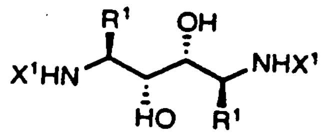
This invention comprises compounds having the structures particularly pointed out in the claims and described hereinafter which bind to retroviral proteases. These compounds are inhibitors of viral protease and are useful for treating disease related to infection by viruses.

This invention is also a pharmaceutical composition, which comprises an aforementioned compound and a pharmaceutically acceptable carrier therefor.

This invention further constitutes a method for treating viral diseases, which comprises administering to a mammal in need thereof an effective amount of an aforementioned inhibitor compound.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention have the structure of formula I:



(I)

wherein X^1 is A-$(B)_n$- where n = 0-2; and

B is, independently, an α-amino acid chosen from the group: Ala, Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr, Tyr, Val, His, or trifluoroalanine, wherein the amino group of B is bonded to A or the carboxy group of the adjacent residue B, whichever is appropriate, and the carboxy group of B is bonded to the amino group of the adjacent residue B or the structure, whichever is appropriate; and

A is covalently attached to the amine group of the adjacent residue B or to the amine group of the structure if n=0, and is:

1) trityl,

2) hydrogen,

3) C_1-C_6 alkyl,

4) R^3-CO- wherein R^3 is:

a) hydrogen,

b) C_1-C_6 alkyl, unsubstituted or substituted with one or more hydroxyl groups, chlorine atoms, or fluorine atoms,

c) phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4, wherein R^4 is:

i) C_1-C_4 alkyl,

ii) halogen, where halogen is F, Cl, Br or I,

iii) hydroxyl,

iv) nitro,

v) C_1-C_3 alkoxy, or

vi) -CO-N$(R^{10})_2$ wherein R^{10} is, independently, H or C_1-C_4 alkyl; or

d) a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;

5) phthaloyl wherein the aromatic ring is unsubstituted or substituted with one or more substituents R^4;

6) $R^5(R^6R^7C)_m$-CO- wherein m = 1-3 and R^5, R^6, and R^7 are independently:

a) hydrogen,

b) chlorine or fluorine,

c) C_1-C_3 alkyl unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups,

d) hydroxyl,

e) phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4,

f) C_1 - C_3 alkoxy,

g) a 5-7 member heterocycle, or

h) R^5, R^6, and R^7 may be independently joined to form a monocyclic, bicyclic, or tricycle ring system each ring of which is C_3-C_6 cycloalkyl;

7) $R^5(R^6R^7C)m$ W- wherein m = 1-3 and W is OCO or SO_2 and R^5, R^6, and R^7 are as defined above, except R^5, R^6, and R^7 are not chlorine, fluorine or hydroxyl if they are adjacent to W;

8) R^8-W- wherein R^8 is a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;

9) R^9-W- wherein R^9 is phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4;

10) R^5-$(R^6R^7C)m$-P(O)(OR^{11})- wherein R^{11} is C_1 - C_4 alkyl or phenyl;

11) R^8-P(O)(OR^{11})-; or

12) R^9-P(O)(OR^{11})-;

-R^1 is:

1) -CH_2R^{12} wherein R^{12} is

a) NH-A wherein A is defined as above;

b) R^5-$(R^6R^7C)m$-;

c) R^5-$(R^6R^7C)m$ V- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-$(R^6R^7C)m$-S(O)n- wherein m = 1-3 and n = 0-2 and R^5, R^6 and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-S(O)n-,

f) R^9-S(O)n-,

g) (R^{13}O)P(O)(OR^{14})- wherein R^{13} and R^{14} are, independently:

i) C_1-C_6 alkyl,

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) R^{13}P(O)(OR^{14})-,

i) $N(R^{10})_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH_2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

2) hydrogen,

3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

4) C_3-C_7 cycloalkyl;

and pharmaceutically acceptable salts thereof.

Peptide compounds of the foregoing description are preferred which are C2 symmetric wherein X^1=X^2, and R^1=R^2.

Suitably R^1 is C_1-C_6 alkyl, benzyloxymethyl, 3-phenylpropyl or benzyloxy. In particular, R^1 may be benzyloxymethyl or 3-phenylpropyl. Preferably R^1 is benzyl.

Suitably X^1 is CbzAla, AlaAla, Val, CbzVal, Cbz or hydrogen.

The compounds of this invention are useful in the manufacture of a medicament, in particular, for a medicament for treating infection by retroviruses.

C_2 symmetric peptide compounds wherein R_1 and R_2 are C_1-C_6 alkyl or aralkyl and X^1 and X^2 are single amino acids or mono- or dipeptides; these groups may be terminally substituted by common acyl groups or blocking groups commonly used in peptide synthesis, such as t-Boc or Cbz, are also preferred.

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the parent drug.

As used herein except where noted, the term "alkyl" refers to a straight or branched chain alkyl radical of the indicated number of carbon atoms including, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl, and the like; "alkoxy" represents an alkyl group of the indicated number of carbon atoms attached through a bridging oxygen atom; "cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; "alkenyl" is meant to include either straight or branched hydrocarbon chains containing one or more carbon-carbon double bonds which may occur at any stable point along the chain, such as ethenyl propenyl, butenyl, pentenyl, 2-methyl propenyl, and the like; "alkynyl" refers to either a straight or branched hydrocarbon chain of the indicated number of carbon atoms which contains a carbon-carbon triple bond which may occur at any stable point along the chain, such as ethynyl, 2-propynyl, 2-butynyl, 4-pentynyl, 2-methyl-3propynyl, and the like.

As used herein except where noted, the term "heterocycle" represents a stable 5- to 7-membered mono- or bicyclic heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, furyl, tetrahydrofuryl,tetrahydropyranyl, thienyl, thiamorpholinyl sulfoxide, thiamorpholinyl sufone, and oxadiazolyl.

When any variable (e.g., A, B, R^1, R^3, ..., R^{17}, heterocycle, substituted phenyl, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By convention used herein, a geminal diol, for example when R6 and R7 are simultaneously hydroxyl, is meant to be equivalent with a carbon-oxygen double bond.

Other abbreviations and symbols commonly used in the art used herein to describe the peptides include the following:

Amino acid	three letter code	Amino acid	three letter code
Alanine	Ala	Leucine	Leu
Arginine	Arg	Lysine	Lys
Asparagine	Asn	Methionine	Met
Aspartic Acid	Asp	Phenylalanine	Phe
Cysteine	Cys	Proline	Pro
Glutamine	Gln	Serine	Ser
Glutaminic Acid	Glu	Threonine	Thr
Glycine	Gly	Tryptophan	Trp
Histidine	His	Tyrosine	Tyr
Isoleucine	Ile	Valine	Val
Asparagine or Aspartic Acid			Asx
Glutamine or Glutamic Acid			Glx

In accordance with conventional representation, the amino terminus is on the left and the carboxy terminus is on the right. All chiral amino acids (AA) can occur as racemates, racemic mixtures, or individual enantiomers or diasteriomers, with all isomeric forms being included in the present invention. β-Ala refers to 3-amino propanoic acid. -Boc refers to the t-butyloxycarbonyl radical, Cbz refers to the carbobenzyloxy radical, i-Bu refers to isobutyl, Ac refers to the acetyl, Ph refers to phenyl, DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, HOBT refers to 1-hydroxybenzotriazole, NMM is N-methylmorpholine, DTT is dithiothreitol, EDTA is ethylenediamine tetraacetic acid, DIEA is diisopropyl ethylamine, DBU is 1, 8 diazobicyclo [5.4.0] undec-7-ene, DMSO is dimethylsulfoxide, DMF is dimethyl formamide and THF is tetrahydrofuran. HF refers to hydrofluoric acid and TFA refers to trifluoroacetic acid.

The peptide moieties denoted by X^1 and X^2 are generally dipeptides or smaller. However, longer peptides which encompass the residues defined herein are also believed to be active and are considered within the scope of this invention.

The selection of residues or end groups may be used to confer favorable biochemical or physico-chemical properties to the compound. The use of hydrophilic residues may be used to confer desirable solubility properties or D-amino acids at the carboxy terminus may be used to confer resistance to exopeptidases.

Synthesis of compounds represented by the structure I can be achieved by pinacol coupling of N-protected alpha-amino aldehydes, $P^2NHCH(R^1)CHO$. One representative procedure involves addition of the aldehyde to a mixture of $TiCl_4$ and magnesium-mercury amalgam in an inert solvent such as THF under inert atmosphere, as described by E. J. Corey, R. L. Danheiser, and s. Chandrasekaran, J. Org. Chem. 41, 260-266 (1976). The

required N-protected alpha-amino aldehydes are readily prepared from the respective N-protected alpha-amino acids $P^2NHCH(R^1)CO_2H$, for example by reduction of the corresponding esters with diisobutyl aluminum hydride, by reduction of derived N-methyl, N-methoxy amides $P2NHCH(R^1)CONMe(OMe)$ with $LiAlH_4$ (Fehrentz and Castro, Synthesis 676 (1983)), or by reduction to the N-protected alpha-amino alcohol followed by oxidation with DMSO-$(COCl)_2$ or SO_3-pyridine (Review: Jurczak and Golebiowski, Chem. Rev. 89, 149 (1989)). Generally the amino protecting group, P^2, is t-Boc-, Cbz-, p-toluenesulfonyl or another standard protecting group chosen as well know in the peptide art. Subsequent to pinacol coupling the protecting group P^2 can be removed and groups X^1 can be introduced. The foregoing procedures can be used to prepare all of the stereoeoisomers of compounds represented by the structure.

Alternatively, compounds represented by the structure I can be prepared from D-(+)-mannitol by conversion to the diaziridine (compound **B**, Scheme 1). The resulting diaziridine is reacted with appropriate nucleophiles such as $(CH_3)_2CuLi$, to introduce the side-chain groups R^1 as illustrated in Scheme 1 and as detailed in the Examples. The preparation of compound **B** has been disclosed by Y. Le Merrer et al., Heterocycles 25, 541 - 548 (1987) and by A. Dureault, C. Greck and J.C. Depezay, Tet. Letters 27, 4157-4160 (1986). This procedure is especially suited to the preparation of compounds the structure where $R^1 = CH_2R^{12}$ where R^{12} is hydrogen or is a group that forms a stable and reactive cuprate reagent, such as methyl, butyl, isopropyl, or other alkyl, alkenyl or aryl which is optionally substituted, for example with fluorine or alkoxy or protected hydroxyl.

Alternatively, compounds represented by the structure I can be prepared from D-(+)-mannitol by conversion to 1,6-ditosyl-3,4-(O-isopropylidene)mannitol as shown in Scheme 1, followed by treatment with a base such as KH or KOtBu in an inert solvent such as THF or ether to yield the diepoxide, 1,2:5,6-dianhydro-3,4-(O-isopropylidene)mannitol (compound **C**, Scheme 2). This diepoxide is reacted with appropriate carbon nucleophiles such as cuprate reagents $(R^{12})_2CuLi$ or alkynylaluminum reagents to introduce the side-chain groups R^1 (Scheme 2). This procedure is also especially suited to the preparation of compounds I where $R^1 = CH_2R^{12}$ where R^{12} is a group that forms a stable and reactive cuprate reagent, as described above. The resulting diol product is converted to the corresponding diamine with inversion of configuration at the alcohol carbons. One way in which this is accomplished is via conversion of the diol to the dimesylate, by reaction with methanesulfonyl chloride and triethylamine, followed by displacement with NaN_3 in DMF to provide the substituted 2,5-diazido-3,4-(O-isopropylidenediol)hexane; conversion to the 2,5-diamino derivative follows by reduction with a hydride reagent such as $LiAlH_4$ or by catalytic hydrogenation with a catalyst such as Pd(O) or Raney-Ni to provide the core structure I (as the isopropylidene derivative)

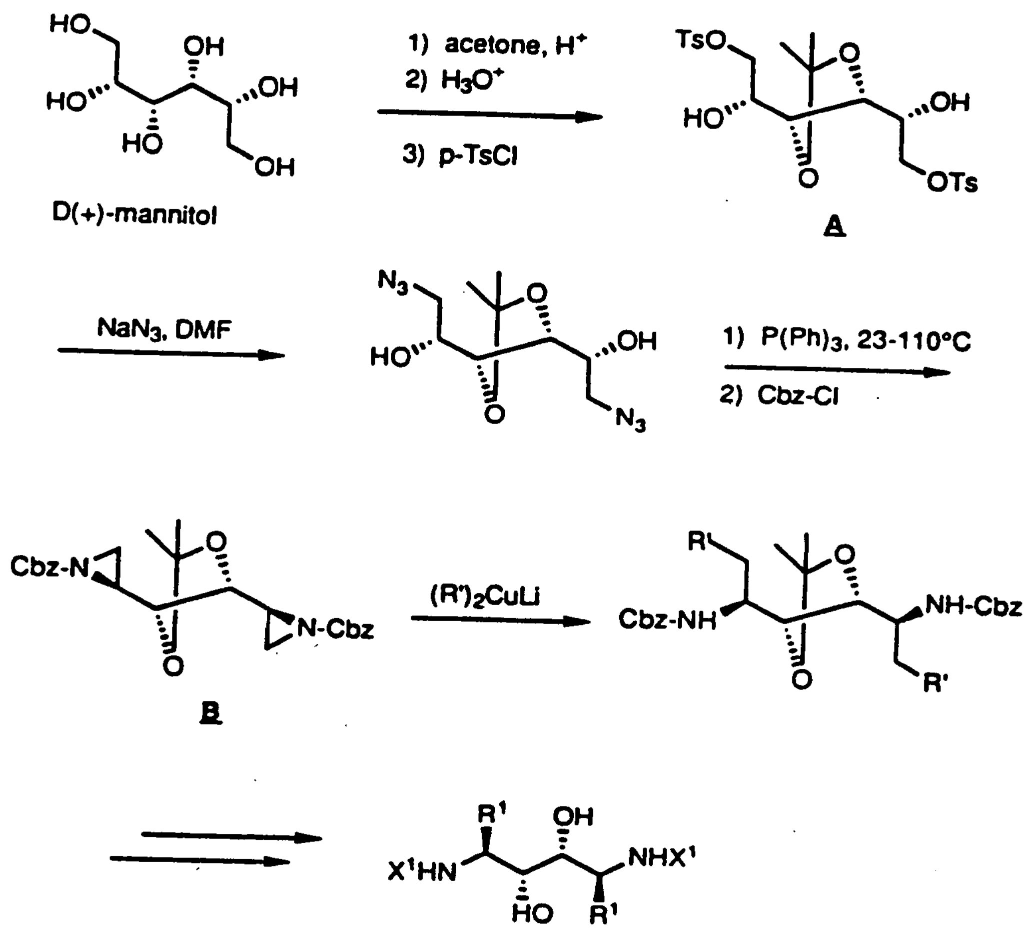
(Scheme 2). Introduction of the groups X^1 is accomplished by standard condensation reactions as are well known in the art.

Compounds of the structure I in which R^{12} is NH-A can be prepared from the diepoxide C or the ditosylate (compound A, Scheme 2) by reaction with NaN_3 in DMF to provide the resulting dihydroxy terminal diazide, which is converted to the corresponding tetraazide with inversion of configuration at the alcohol carbons as described above, and subsequently to the corresponding tetramine. Selective reaction of the terminal amines with groups A or with protecting groups such as Boc or Cbz is then followed by introduction of the groups $X^1 = X^2$. In a related fashion, groups $R^1 = R^2$ in compounds in which R^1 is $N(R^{10})_2$, $NR^{15}R^{16}$, R^5-$(R^6R^7C)m$ V- or R^5-$(R^6R^7C)m$-S(O)n-can be introduced by reaction of diepoxide C with the appropriate oxygen, nitrogen, or thiol nucleophile, with subsequent thiol oxidation as necessary. Reaction of diepoxide C with the appropriate phosphorus nucleophile in an Arbuzov or Michaelis-Arbuzov reaction allows introduction of groups $R^1 = R^2$ which are $(R^{13}O)P(O)(OR^{14})$- or $R^{13}P(O)(OR^{14})$-.

Either enantiomer of compounds of the structure can be prepared from the respective enantiomer of mannitol by the procedures shown in Schemes 1-2.

Scheme 1

Synthesis of General Structure I



I

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) $R^{13}P(O)(OR^{14})$-,

i) $N(R^{10})_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

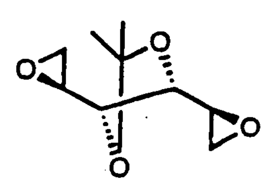
2) hydrogen,

3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

4) C_3-C_7 cycloalkyl, and

R" and R"' are hydrogen, an amino-protecting group or taken together are N_2, which comprises

1) reacting a compound of the formula:



with a compound R'-Z, wherein Z is a moiety which renders R' nucleophilic.

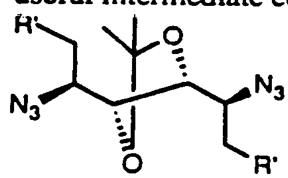
2) converting the resulting hydroxy groups to displaceable groups,
3) reacting the displaceable groups with a nitrogen nucleophile.

Typically Z is hydrogen, an alkali metal, such as Li, Na or K, or an earth metal, such as magnesium, or a transition metal, such as copper, aluminum, titanium, zinc or cadmium, or a species derived therefrom. Representative of R'-Z are optionally substituted alkyl, aryl or heteroaryl lithium, alkyl, aryl or heteroaryl magnesium halides (eg. Grignard reagents), lithium dialkyl cuprate, lithium diaryl cuprate, or the alkali metal salts of optionally substituted alkyl alcohols, phenols or benzyl alcohols. Lithium diphenyl cuprate is especially useful.

The hydroxyls are converted to suitable displaceable groups, such as mesylate, tosylate, brosylate, benzoate, acetate and halide, by methods common in the art. The tosyl group is especially suitable and is formed by reacting the hydroxyl groups with tosyl chloride, for instance.

Suitable nitrogen nucleophiles are those which are able to react with a displaceble group. Unhindered organic amines or heterocyles, metal salts of amines, heterocycles or azide are useful. Generally an nitrogen containing group of the formula R'''R'vN-Z, wherein Z is as defined above and R''' and R'v are hydrogen, an amino-protecting group or taken together are N_2 (eg. azide) are useful. A metal azide, such as sodium or potassium azide, is preferable. Subsequent reduction of the azido groups provides amino groups.

Particularly useful intermediate compounds of this invention are:



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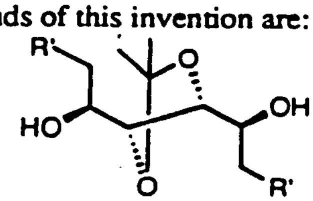


(IV)

wherein R' is 1) R^{12}, as defined for formula I, 2) hydrogen, 3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups or 4) C_3-C_7 cycloalkyl.

The compounds of this invention are prepared by the solid phase technique of Merrifield (J. Am. Chem. Soc., 85, 2149 (1964), or preferably by solution methods known to the art. A combination of solid phase and solution synthesis may be used, as in a convergent synthesis in which di-, tri-, or tetra-peptide fragments may be prepared by solid phase synthesis and either coupled or further modified by solution synthesis. The methods of peptide synthesis generally set forth in J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", Pierce Chemical Company, Rockford, Il (1984) or M. Bodonsky, Y.A. Klauser and M. A. Ondetti, "Peptide Synthesis", John Wiley & Sons, Inc., New York, N.Y. (1976), or "The Peptides" gross and Meienhoffer, eds.; Acad. Press, 1979. Vols I-III, may be used to produce the peptides of this invention and are incorporated herein by reference.

Each amino acid or peptide is suitably protected as known in the peptide art. For example, the Boc- or carbobenzyloxy-group is preferred for protection of the amino group, especially at the α position. A benzyl group or suitable substituted benzyl group is used to protect the mercapto group of cysteine, or other thiol containing amino acids; or the hydroxyl of serine or threonine. The tosyl or nitro group may be used for protection of the guanidine of Arg or the imidazole of His, and a suitably substituted carbobenzyloxy group or benzyl group may be used for the hydroxyl group of Tyr, Ser or Thr, or the ε-amino group of lysine. Suitable substitution of the carbobenzyloxy or benzyl protecting groups is ortho and/or para substitution with chloro, bromo, nitro or methyl, and is used to modify the reactivity of the protective group. Cysteine and other sulfur-containing amino acids may also be protected by formation of a disulfide with a thioalkyl or thioaryl group. Except for the Boc group, the protective groups are, most conveniently, those which are not removed by mild acid treatment. These protective groups are removed by such methods as catalytic hydrogenation, sodium in liquid ammonia or HF treatment as known in the art.

If solid phase methods are used, the peptide is built up sequentially starting from the carboxy terminus and working toward the amino terminus of the peptide. Solid phase synthesis is begun by covalently attaching the C terminus of a protected amino acid to a suitable resin, such as a benzhydrylamine resin (BHA), methylbenzhydrylamine resin (MBHA) or chloromethyl resin (CMR), as is generally set forth in U.S. Patent No. 4,244,946. A BHA or MBHA support resin is used for the carboxy terminus of the product peptide is to be a carboxamide. A CMR support is generally used for the carboxy terminus if the produced peptide is to be a carboxyl group, although this may also be used to produce a carboxamide or ester.

Modification of the terminal amino group of the peptide is accomplished by alkylation or acetylation as is generally known in the art. These modifications may be carried out upon the amino acid prior to incorporation into the peptide, or upon the peptide after it has been synthesized and the terminal amino group liberated, but before the protecting groups have been removed.

Typically, acetylation is carried out upon the free amino group using the acyl halide, anhydride or activated ester, of the corresponding alkyl acid, in the presence of a tertiary amine. Mono-alkylation is carried out most conveniently by reductive alkylation of the amino group with an appropriate aliphatic aldehyde or ketone in the presence of a mild reducing agent, such as lithium or sodium cyanoborohydride. Dialkylation as well as quaternization may be carried by treating the amino group with an excess of an alkyl halide in the presence of a base.

Solution synthesis of peptides is accomplished using conventional methods used to form amide bonds. Typically, a protected Boc-amino acid which has a free carboxyl group

is coupled to a protected amino acid which has a free amino group using a suitable carbodiimide coupling agent, such as N, N' dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBT) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a protected Boc-amino acid, and subsequent reaction with the free amine of a protected amino acid, optionally in the presence of a base, are also suitable. For example, a protected Boc-amino acid or peptide is treated in an anhydrous solvent, such as methylene chloride or tetrahydrofuran (THF), in the presence of a base, such as N-methyl morpholine, or a trialkyl amine, with isobutyl chloroformate to form the mixed anhydride, which is subsequently reacted with the free amine of a second protected amino acid or peptide. The peptide formed by these methods may be deprotected selectively, using conventional techniques, at the amino or carboxy terminus and coupled to other peptides or amino acids using similar techniques. After the peptide has been completed, the protecting groups may be removed as hereinbefore described, such as by hydrogenation in the presence of a palladium or platinum catalyst, treatment with sodium in liquid ammonia, hydrofluoric acid, trifluoroacetic acid or alkali.

Esters are often used to protect the terminal carboxyl group of peptides in solution synthesis. They may be converted to carboxylic acids by treatment with an alkali metal hydroxide or carbonate, such as potassium hydroxide or sodium carbonate, in an aqueous alcoholic solution. The acids may be converted to other esters via an activated acyl intermediate as previously described.

The amides and substituted amides of this invention are prepared from carboxylic acids of the peptides in much the same manner. Thus, ammonia or a substituted amine may be reacted with an activated acyl intermediate of an amino-protected α-amino acid or oligopeptide to produce the amide. Use of coupling reagents, such as DCC, is convenient for forming substituted amides from the carboxylic acid itself and a suitable amine.

In addition, the methyl esters of this invention may be converted to the amides, or substituted-amides, directly by treatment with ammonia, or a substituted amine, in methanol solution. A methanol solution of the methyl ester of the peptide is saturated with ammonia and stirred in a pressurized reactor to yield the simple carboxamide of the peptides. Procedures for the determination of the inhibition constant (Ki) by Dixon analysis are described in the art, e.g., in Dreyer, et al. Proc. Natl. Acad. Sci. U.S.A., 86, 9752-9756 (1989). A peptidolytic assay is employed using the substrate Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH_2 and recombinant HIV protease as in Stricker, et al., Proteins, 6, 134-154 (1989). The lower Ki value indicates a higher binding affinity.

Pharmaceutical compositions of the compounds of this invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other

pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipient such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

A preferred composition for parenteral administration may additionally be comprised of a quantity of the compound encapsulated in a liposomal carrier. The liposome may be formed by dispersion of the compounds in an aqueous phase with phospholipids, with or without cholesterol, using a variety of techniques, including conventional handshaking, high pressure extrusion, reverse phase evaporation and microfluidization. A suitable method of making such compositions is more fully disclosed in copending Application Serial No. 06/763,484 and is incorporated herein by reference. Such a carrier may be optionally directed toward its site of action by an immunoglobulin or protein reactive with the viral particle or infected cells. The choice of such proteins would of course be dependent upon the antigenic determinants of the infecting virus. An example of such a protein is the CD-4 T-cell glycoprotein, or a derivative thereof, such as sCD-4 (soluble CD-4), which is reactive with the glycoprotein coat of the human immunodeficiency virus (HIV). Such proteins are disclosed in copending Application Serial No. 07/160,463, which is incorporated herein by reference. Similar targeting proteins could be devised, by methods known to the art, for other viruses and are considered within the scope of this invention.

Alternatively, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup or oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline and water. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, a pulverized powder of the compounds of this invention may be combined with excipient such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository. The pulverized powders may also be compounded with an oily preparation, gel, cream or emulsion, buffered or unbuffered, and administered through a transdermal patch.

This invention is also a method for treating viral infection, particularly infection by retroviruses, which comprises administering a compound of formula I to a patient infected with a susceptible virus. The method is particularly applicable to infection by the Human Immunodeficiency Virus, type 1. When the compounds of this invention are used to induce anti-viral activity in patients which are infected with susceptible viruses and require such treatment, the method of treatment comprises the administration orally, parenterally, bucally, trans-dermally, intravenously, intramuscularly, rectally or by insufflation, of an effective quantity of the chosen compound, preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are selected from the range of 0.05 to 50 mg/kg of body weight. Dosage units will typically be from 50 to 1000 mg. These dosage units may be administered one to ten times daily for acute or chronic infection. The dosage will be readily deterimined by one skilled in the art and will depend upon the age, weight and condition of the patient, and the route of administration. Combination therapy as described in Eur. Pat. Appl. No. 337 714 at pages 42-47 are included herein.

The Examples which follow serve to illustrate this invention. The Examples are intended to in no way limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

In the Examples, all temperatures are in degrees Celsius. Amino acid analyses were performed upon a Dionex Autoion 100. Analysis for peptide content is based upon Amino Acid Analysis. FAB mass spectra were performed upon a VG Aab mass spectrometer using fast atom bombardment. NMR spectra were recorded at 250 MHz using a Bruker Am 250 spectrometer. Multiplicities indicated are: s=singlet, d-doublet, t-triplet, q-quartet, m-multiplet and br indicates a broad signal.

Purification of Recombinant HIV Protease

Methods for expressing recombinant HIV protease in E.coli have bee described by Debouck, et al., Proc. Natl. Acad. Sci. USA, 84, 8903-6 (1987). The enzyme used to assay the compounds of this invention was produced in this manner and purified from the cell pellet as previously described by Stickler et al. Proteins, 6, 139-154 (1989).

EXAMPLES

The following compounds were prepared from D-mannitol as described by LeMerrer et al., Heterocycles, 25, 541-548 (1987):

1) 1,6-di-0-tosyl-3,4-Oisopropylidene-D-mannitol (Compound **A**)

2) (2S, 3R, 4R, 5S)-1,2:5,6-di-(N-carbobenzyloxyimino)-3,4-(0-isopropylidene)-hexanediol (Compound **B**)

3) 1,2:5,6-dianhydro-3,4-O-isopropylidene-D-mannitol (Compound **C**).

Example 1

Preparation of (1S, 2R, 3R, 4S)-carbobenzyloxyalanylalanyl-N-(1-ethyl-2,3-dihydroxy-4-(carbobenzyloxyalanylalanyl)amino)hexyl-amide 2.

a) (1S, 2R, 3R, 4S)-carbobenzyloxy-N-(1-ethyl-2,3-(0-isopropylidenediol)-4-carbobenzyloxyamino)hexyl-amide **3**.

Methyl lithium (18.9 mL, 23.6 mmol; 1.25 M in ether) was added slowly to a slurry of CuI (2.24 g, 11.8 mmol) in THF (25 mL) at -10°C for 15 min, then was cooled to -78°C. A solution of compound **B** (265 mg, 0.59 mmol) in THF (2 mL) was added, and the mixture was maintained at -25°C overnight without stirring. The mixture was diluted with a solution of saturated NH_4Cl (100 mL) and concentrated aqueous NH_3 (10 mL), and extracted with ethyl acetate (3x25 mL). Concentration and flash chromatography of the residue (gradient elution, 0% to 16% ethyl acetate in hexanes), provided the titled compound (143 mg, 50% yield).

b) (1S, 2R, 3R, 4S)-carbobenzyloxyalanylalanyl-N-(1-ethyl-2,3-(0-isopropyl-idenediol)-4-(carbobenzyloxyalanylalanyl)amino)hexyl-amide **4**

A solution of **3** (135 mg, 0.28 mmol) is methanol (10 mL) was stirred with 10% Pd on carbon (70 mg) under and H_2 atmosphere for 4 hr. The mixture was filtered and concentrated, and the residue was combined with DMF (5 mL), carbobenzyloxyalanylalanine (165 mg, 0.56 mmol), HOBT (76 mg, 0.56 mmol), and DCC (116 mg, 0.56 mmol). The solution was stirred for 24 hr, then was filtered, diluted with ethyl acetate (50 mL) and washed with water (2x20 mL). Concentration and flash chromatography of the residue (gradient, 0% to 8% methanol in CH_2Cl_2) provided the titled compound (196 mg, 91%).

c) (1S, 2R, 3R, 4S)-carbobenzyloxyalanylalanyl-N-(1-ethyl-2,3-dihydroxy-4-(carbobenzyloxyalanylalany)amino)hexyl-amide **2**.

A solution of **4** (191 mg, 0.25 mmol) in 70% acetic acid (20 mL) was stirred at 50°C for 24 hr, then was concentrated under vacuum. The residue was dissolved in ethyl acetate and washed successively with 5% $NaHCO_3$, water, and brine, then was dried over Na_2SO_4 and concentrated to a solid. The residue was triturated with CH_2Cl_2 and filtered to provide the titled compound **2** (105 mg, 58%) wherein R^1 is ethyl and X^1 is Cbz-AlaAla. Anal. Calc. for $C_{36}H_{52}N_6O_{10}$: C, 59.33; H, 7.19; N, 11.53. Found: C, 59.11; H, 7.40; N, 11.19.

Example 2

Preparation of (1S, 2R, 4S)-alanylalanyl-N-(1-ethyl-2,3-dihydroxy-4- (alanylalanyl)-amino)hexyl-amide dihydrochloride 5.

A solution of compound **2** (24.3 mg) in methanol (3 mL) was stirred with 10% Pd on carbon (13 mg) under an H_2 atmosphere for 2 hr. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in 0.1 N HCl (10 mL), washed with ethyl acetate, and lyophilized to provide the titled compound 5 (26 mg.) wherein R^1 is ethyl and X^1 is AlaAla. MS (DCI): m/z 461(M+H)+.

Example 3

Preparation of (1S, 2R, 3R, 4S)-carbobenzyloxyalanylalanyl-N-(1-(2- methyl)propyl-2,3-dihydroxy-4-(carbobenzyloxyalanylalanyl)amino-6-methyl)heptyl-amide 9.

(a) (1S, 2R, 3R, 4S)-carbobenzyloxy-N-(1-(2-methyl)propyl-2,3- (O-isopropylidenediol)-4-carbobenzyloxyamino-6-methyl)heptyl-amide 7.

To a mixture of anhydrous LiBr (0.989 g, 11.5 mmol) an CuBr (1.65 g, 11.5 mmol) in THF (10 mL) at -60°C under Ar was added isopropylmagnesium chloride (12.7 mL, 1.8 M in THF, 23 mmol) with stirring. After 20 min, a solution of compound **B** (0.52 g, 1.15 mmol) in THF (6 mL) was added. The mixture was stirred at - 50°C for 2 hr, then was left at -25 °C overnight. The mixture was diluted with saturated aqueous NH_4Cl (100 mL) and 14% aqueous ammonia (20 mL), then extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with water (50 mL) and concentrated, and the residue was purified by flash chromatography (gradient, 0 to 8% ethyl acetate in hexanes) to provide the titled compound (0.27 g, 27%).

(b) (1S, 2R, 3R, 4S)-carbobenzyloxyalanylalanyl-N-(1-(2-methyl)propyl-2,3-(O-isopropylidenediol)-4- (carbobenzyloxyalanylalanyl)amino-6-methyl)heptyl-amide 8.

The titled compound was prepared in 46% yield from compound 7 by the procedure described in Example 1(b). MS (FAB): m/z 825.4 $(M+H)^+$.

(c) (1S, 2R, 3R, 4S)-carbobenzyloxyalanylalanyl-N-1-(2-methyl)propyl-2,3-dihydroxy 4-(carbobenzyloxyalanylalany)amino-6-methyl)heptyl-amide 2.

Compound 8 (0.22 g, 0.27 mmol) was deprotected by the procedure described in Example 1, Part (b), to yield the titled compound (89 mg, 0.113 mmol, 42% yield) wherein R^1 is isobutyl and X^1 is Cbz-AlaAla. mp 220-221°C. Anal. Calc. for $C_{40}H_{60}N_6O_{10}$: C, 61.21; H, 7.70; N, 10.71. Found: C, 60.91; H, 7.61; N, 10.58.

Example 4

Preparation of (1S, 2R, 3R, 4S)-alanylalanyl-N-(1-(2-methyl)propyl-2,3- dihydroxy-4-(alanylalanyl)amino-6-methyl)heptyl-amide dihydrochloride 10.

The titled compound (17mg) wherein R^1 is isobutyl and X^1 is AlaAla was prepared from compound 9 (44 mg) by the procedure of Example 2.

Example 5

Preparation of (1S, 2R, 3R, 4S)-carbobenzyloxyalanyl-N-(1-(2-methyl)propyl-2,3-dihydroxy-4-(carbobenzyloxyalanyl)amino-6-methyl)heptyl-amide 11.

The titled compound wherein R^1 is isobutyl and X^1 is Cbz-Ala was prepared from compound 7 as described in Example 3, Parts (b)-(c), except substituting carbobenzyloxyalanine in place of carbobenzyloxyalanylalanine. mp 169-170°C. MS (DCI/NH3): m/z 643 (M+H)+. Anal. Calc. for $C_{25}H_{50}N_4O_8$: C, 63.53; H, 7.84; N, 8.72. Found: C, 64.01; H, 8.21;N,9.11.

Example 6

Preparation of (2S,3R,4R,5S)-1,6-diphenyl-2,5-bis(benzyloxycarbonylvalinyl-amino)hexane-3,4-diol 18.

a) (2R,3R,4R,5R)-1,6-diphenyl-3,4-(isopropylidenedioxy)hexane-2,5-diol 12

To a suspension of 865 mg (4.5 mmol) of copper(1) iodide in 10 mL of ether at -78° was added a solution of 5 mL of phenyl lithium in cyclohexane (9 mmol). The reaction mixture was slowly warmed to - 40° and recooled to -78°. To this dark brown mixture was added a solution of 435 mg (2.33 mmol) of bisepoxide C in 10 mL of ether via syringe. After stirring at -78° for 2 h, the reaction mixture was allowed to warm to room

temperature and stirred overnight. Quenched with 1:1 mixture of saturated ammonium chloride and 30% ammonium hydroxide. extracted with ether, washed with ammonium chloride until the blue color completely disappeared. The solvents were dried over anhydrous sodium sulfate and removed in vacuo. The residual oil was flash chromatographed (silica, ethyl acetate, hexane 1:8) to give 691 mg (87%) of 2 as a slight yellow oil. ^{1}HNMR (CDCl3, 250 MHz) δ 7.4 (m, 10 H), 3.7 (m, 4H), 3.1 (dd, 2H, J= 2, 14 Hz), 3.0 (s, 2H), 2.7 (dd, 2 H, J= 7, 14 Hz), 1.4 (s, 6 H).

b) (2R,3R,4R,5R)-1,6-diphenyl-3,4-(isopropropylidenedioxy)-2,5-bis(tosyloxy)hexane 13

To a solution of 300mg (0.8 mmol) of the diol 12 in 5mL of pyridine at 0° was added 1.5g (7.8 mmol) of p-toluenesulfonyl chloride. After stirring at 0° for 2h the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was poured into 15 mL of ice cold 6 N hydrochloric acid, extracted with methylene chloride, washed with 3% sodium bicarbonate and solvents removed in vacuo. MPLC, silica, ethyl acetate: hexane 1:10 gave 520 mg (92 %) of the ditosylate 13 as a an oil. MS(DCI, NH_3) $(M+NH_4)^+$ 668.5; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.5-7.0 (m, 10 H), 4.9 (m, 2 H), 4.3 (s, 2 H), 3.0 (dd, J= 2, 4 Hz), 2.35 (s, 6H), 1.5 (s, 6 H).

c) (2S,3R,4R,5S)-1,6-diphenyl-3,4-(isopropylidenedioxy)-2,5-bisazido-hexane 14

To a solution of 355 mg (0.54 mmol) of bistosylate 3 in 5 mL of dimethyl formamide was added 975 mg (15 mmol) of sodium azide. The reaction mixture was heated at 90° for 8 h and then at 105° for 6 h. The reaction is cooled and the unreacted sodium azide was filtered off, washed with ether and solvents were removed in vacuo. The residue was chromatographed over silica gel (ethyl acetate : hexane 1:20) to give 180 mg (89%) of an oil as a mixture of the titled product 14 and an elimination product, (3R,4R,5S)-1,6-diphenyl-3,4-(isopropylidenedioxy)-5-azido-hex-1-ene 15, in the ratio 4.6:1 as evidenced by ^{1}HNMR. This mixture was found to be inseparable by chromatography. MS(DCI, NH_3) of 14 $[M+NH_4^+]$ 410.5; ^{1}HNMR (characteristic peaks for the bis azide 14) δ 7.4-7.2 (m, 10 H), 4.1 (s 2H), 2.8 -3.4 (m, 6 H), 1.5 (s, 6 H) and the characetristic peaks for the elimination product 15 δ 6.72 (d, 1 H, J= 14 Hz), 6.05 (dd, 1H, J= 6, 14 Hz), 4.65 (t, 1H, J= 7 Hz), 3.75 (dd, 1H, J= 2, 7 Hz), 3-3.4 (m, 5 H), 1.4 (s, 3H), 1.6 (s, 3H).

d) (2S,3R,4R,5S)-1,6-diphenyl-3,4-(isopropylidenedioxy)hexane-2,5-diamine 16

180 mg of a mixture of azides produced in the previous experiment was subjected to hydrogenation at 1 atm over 100 mg of Pearlman's catalyst (10 % $Pd(OH)_2$ on C). After 10 h, the catalyst was filtered through celite and washed with ether and solvents

removed in vacuo to give 124 mg (73 %) of mixtures of amines. Pure diamine **16** was obtained by chromatography over florisil (ether followed by methanol). MS(DCI, NH3) $(M+H)^+$ 341.5; ^{1}HNMR (CD_3OD, 250 MHz) δ 7.4-7.0 (m, 10 H), 3.9 (bs, 2H), 3.0 (bt, 2 H), 2.6 (m, 4H), 1.4 (s, 6 H).

e) (2S,3R,4R,5S)-1,6-diphenyl-2,5-bis(benzyloxycarbonylvalinylamino)-3,4-(isopropylidenedioxy)hexane **17**

To 100 mg (0.4 mmol) of Cbz-Val in 2 mL of tetrahydrofuran at -40° was added 65 µL (0.59mmol) of N-methylmorpholine followed by 53 µL (0.4 mmol) of isobutyl chloroformate. After stirring at -40° for 15 min a solution of 40 mg (0.12 mmol) of diamine in 4 mL of dimethylformamide was added. The reaction mixture was warmed to room temperature over a period of 2h and stirred overnight. It was diluted with 100 mL of ethyl acetate washed with 2x20 mL of 5% hydrochloric acid, 50 mL of 5% sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of solvents followed by flash chromatography (silica gel, 10% $MeOH/CH_2Cl_2$) gave an oil which on trituration with ether/hexane gave 67 mg (70%) of the adduct **17** as a solid. Anal Calcd for $C_{47}H_{58}N_4O_8$: C(69.95), H(7.24), N(6.94); Found C(69.79), H(7.20), N(6.88); ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.5-7.0 (m, 20 H), 6.1 (br d, 2H), 5.1 (br s, 4 H), 4.9 (br d, 2 H), 4.4 (q, 2 H, J= 7 Hz), 3.75 (dd, 2 H, J= 7 Hz), 3.6 (br s, 2 H), 2.8 (br d, 4 H), 2.0 (m, 2 H), 1.4 (s, 6 H), 0.75 (d, 6 H, J= 7 Hz), 0.6 (d, 6 H, J= 7 Hz).

f) (2S,3R,4R,5S)-1,6-diphenyl-2,5-bis(benzyloxycarbonylvalinylamino)hexane-3,4-diol **18**

33 mg of the acetonide was suspended in 4 mL of 70% acetic acid and heated in an oil bath maintained at 75° for 12 h. During the reaction solid product appears on the sides of the flask. Cooled and 15 mL of methylene chloride was added. The methylene chloride layer was carefully removed using a pipette and solvents removed in vacuo to give 29 mg (88 %) of a solid. Trituration with ether/hexane mixture provided 23 mg of pure diol 8. Anal Calcd for $C_{44}H_{54}N_4O_8$: C(68.91), H (7.09), N(7.31); Found C(68.83), H(7.07), N(7.08); ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.5-7.1 (m, 20 H), 6.25 (d, 2H, J= 7 Hz), 5,1 (s, 4 H), 4.9 (bs, 2 H), 4.1 (q, 2H, J= 7 Hz), 3.8 (two doublets, 4 H, J= 7 Hz), 3.4 (bs, 2H), 2.9 (m, 4 H), 2.0 (m, 2 H), 0.8 (d, 6 H, J= 7 Hz), 0.6 (d, 6 H, J= 7 Hz).

Example 7

Preparation of (4S,5R,6R,7S)-1,10-diphenyl-4,7-bis[N-benzyloxycarbonylvalinyl-amino]decane-5,6-diol 25.

a) (4R,5R6R,7R)-1,10-diphenyl-4.7-dihydroxy-5,6-(isopropylidenedioxy)-decane-1,9-diyne **19**

To a solution of 1.8 g (18 mmol) of phenylacetylene in 20 mL of tetrahydrofuran at -78° was added 10 mL (16 mmol) of a 1.6 M solution of n- BuLi in hexane over a period of 10 min. After stirring for 15 min at -78° 2 mL of borontrifluoride etherate was added and stirred for an additional 15 min. To this mixture was added 650 mg (3.5 mmol) of the diepoxide in 8 mL of tetrahydrofuran. Stirred for 2 h and quenched with saturated ammonium chloride solution. Extracted with ethyl acetate , washed with water dried over anhydrous sodium sulfate and solvents removed in vacuo. The residual oil was flash chromatographed over 50 g silica gel to give 1.36 g(100 %) of **19** as a slight yellow oil. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.5-7.1 (m, 10 H), 3.95 (m, 2H), 3.8 (br s, 2H), 3.35 (br s, 2H), 2.9 (dd, 2H, J= 4, 14 Hz), 2.65 (dd, 2 H, J= 7, 14 Hz), 1.4 (s, 6H).

b) (4R,5R,6R7R)-1,10-diphenyl-4.7-dihydroxy-5,6-(isopropylidenedioxy)-decane **20**

295 mg of the diol obtained above was dissolved in 5 mL of methanol and hydrogenated over 50 mg of 10 % Pd/C. After overnight stirring the catalyst was filtered and washed with ether. Removal of solvents gave 290 mg of **10** as a colorless oil. MS(DCI, NH_3) $(M+H)^+$ 399.4; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.5 -7.1 (m, 10 H), 3.6 (m, 4 H), 3.25 (s, 2H), 2.6 (m, 4 H), 1.4-1.9 (m, 8 H), 1.35 (s, 6H).

c) (4R,5R,6R,7R)-1,10-diphenyl-4.7-bis(p-toluenesulfonyloxy)-5,6-(isopropylidenedioxy)-decane **21**

To a solution of 250 mg (0.628 mmol) of the diol in 2.5 mL of pyridine was added 900mg (4.8 mmol) of p-toluenesulfonyl chloride at 0° and stirred for 1 h. Warmed to room temperature and stirred overnight. The reaction mixture was processed as usual. MPLC (silica, ethyl acetate:hexane, 1:8) gave 220 mg of bistosylate **21** as a colorless oil. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.7-7.0 (m, 18 H), 4.6 (m, 2H), 3.9 (q, 2 H, J= 4Hz), 2.5 (m, 4 H), 2.4 (s, 6H), 1.8-1.3 (m, 8 H), 1.25 (s, 6H).

d) (4S,5R,6R,7S)-1,10-diphenyl-4.7-bisazido-5,6-(isopropylidenedioxy)-decane **22**

220 mg of the ditosylate **11** and 500 mg of sodium azide was suspended in 3 mL of DMF and heated in an oil bath maintained at 95° for 10 h. Cooled and diluted with ether. Unreacted sodium azide was filtered off and the solvents removed in vacuo. The residual oil (85 mg) was found to be sufficiently pure for the next experiment. MS(DCI.NH_3) $(M+NH_4)^+$ 466; ^{1}HNMR (7.4-7.1 (m, 10H), 4.0 (s, 2 H), 2.95 (m, 2 H), 2.6 (m, 4 H), 2.0-1.4 (m, 8 H), 1.4 (s, 6 H).

e) (4S,5R,6R,7S)-1,10-diphenyl-4,7-bisamino-5,6-(isopropylidenedioxy)-decane 23

85 mg of the bisazide was hydrogenated over 40 mg of Pearlman's catalyst in 5 mL of ethyl acetate until the TLC showed complete disappearance of starting material. The catalyst was filtered through celite, washed with methanol and solvents removed in vacuo to give 65 mg (80%) of the diamine 23 as an oil. ^{1}HNMR (CD_3OD, 250 MHz) δ 7.4-7.0 (m, 10 H), 3.7 (m, 2H), 2.6 (m, 6H), 1.7-1.5 (m, 8 H), 1.35 (s, 6H).

f) (4S,5R,6R,7S)-1,10-diphenyl-5,6-(isopropylidenedioxy)-4,7-bis[N-benzyloxycarbonylaminovalinylamino]decane 24

To 100 mg (0.4 mmol) of Cbz-Val in 2 mL of THF at -40° was added 65 μL of N-methylmorpholine and 53 μL of isobutylchlotoformate.

The reaction mixture was stirred for 15 min and a solution of 51 mg (0.128 mmol) of the diamine 23 in 2.5 mL of DMF was added. The mixture was slowly warmed to room temperature and stirred overnight. Diluted with 75 mL of ethyl acetate, washed with 2x25 mL of 5% hydrochloric acid , 50 mL of 3 % sodium bicarbonate and solvents removed in vacuo. The residual oil was flash chromatographed (ethyl acetate: hexane 1:4) to give 69 mg of 24 as a colorless solid. ^{1}HNMR ($CDCl_3$, 250 MHz) δ (7.4-7.0 (m, 20 H), 6.2 (d, 2H, J= 7 Hz), 5.2 (d, 2 H, J= 7 Hz), 5.1 (m, 4 H), 4.1 (m, 2H), 3.9 (m, 2H), 3.5 (bs, 2H), 2.6 (m, 4H), 2.2 (m, 2H), 1.6 (bs, 8H), 1.3 (s, 6 H), 1.0 (d, 6H, J= 7 Hz), 0.9 (d, 6H, J= 7 Hz).

g) (4S,5R,6R,7S)-1,10-Diphenyl-4,7-bis[N-benzyloxycarbonylvalinylamino]decane-5,6-diol 25

A suspension of 23 mg of the acetonide 24 from the previous experiment in 3.2 mL of 70% acetic acid was heated in an oil bath maintained at 90° for 6 h. The reaction mixture was cooled and the solvents removed in vacuo to give 20 mg of 25 as a colorless solid. MS(FAB) $(M+H)^+$ 823.3; ^{1}HNMR (CD_3SOCD_3) δ 7.4-7.0 (m, 20 H), 5.0 (q, 4 H, J= 7 Hz), 4.6 (bs, 2H), 3.8-4.2 (m, 4 H), 3.4 (m, 2H), 2.5 (m, 4H), 2.0 (m, 2H), 1.5 (m, 8 H), 0.8 (two overlapping doublets, 12 H, J= 7 Hz).

Example 8

Preparation of (5S,6R,7R,8S)-5,8-bis[benzyloxycarbonylaminovalinylamino]-dodecane-6,7-diol 32.

a) (5R, 6R, 7R,8R)-5,8-dihydroxy,6,7-(isopropylidenedioxy)dodecadeca-1,11-diene 26

To a suspension of 400 mg of copper (1) iodide in 6 mL of ether at - 60° was added 4 mmol of allylmagnesium bromide via syringe over a period of 3 min. Stirred at -60 for 15 min, cooled to -78 and added 140 mg (0.75 mmol) of the bisepoxide in 4 mL of ether.

Kept at -78 for 1h, and cooling bath removed and the reaction mixture was allowed to warm to room temperature and stirred for 4h. Quenched with 5 mL of sat. ammonium chloride and 10 mL of 30 % ammonium hydroxide. Extracted with ether, washed with ammonium chloride solution and solvents removed in vacuo to give 216 mg (>100 %) of the diol which was found to be sufficiently pure for the next step. ^{1}HNMR($CDCl_3$, 250 MHz) δ 5.3 (m, 2H), 5.0 (m, 4H), 3.5-3.8 (m, 6 H), 2.0-2.4 (m, 4 H), 1.95-1.7 (m, 2H), 1.5-1.6 (m, 2H), 1.3 (s,6H).

b) (5R, 6R, 7R,8R)-5,8-dihydroxy-6,7-(isopropylidenedioxy)dodecadecane **27**

220 mg of the diol **26** was dissolved in 5 mL of methanol and hydrogenated over 20 mg of 10% Pd/C as usual to yield the titled product (210 mg). MS (DCI,NH_3) $(M+NH_4)^+$ 292.4; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 3.95 (s, 2H), 3.2-3.6 (m, 4 H), 1.2-1.8(m,12 H), 1.3 (s, 6 H), 0.8 (t, 6 H, J= 7 Hz).

c) (5R, 6R, 7R,8R)-5,8-diamino,6,7-(isopropylidenedioxy)dodecadecane **30**

215 mg of the bisdiol was dissolved in pyridine and 0.5 mL of methane sulfonyl chloride was added at)°. The reaction mixture was stirred at 0° for 3h, followed by room temperature for overnight. Worked up as usual. 410 mg of a slight brown oil was obtained which was taken directly for the azide formation. The bismesylate **28** displayed the following spectral characteristics. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 4.7 9m, 2H), 4.2 (m, 2H), 3.05 (s, 6H), 1.8 (m, 4 H), 1.2-1.6 (m, 8 H), 1.3 (s, 6 H), 0.9 (t, 6H, J= 7Hz).

The mesylate **28** was dissolved in 5 mL of DMF and 650 mg of sodium azide was added. The reaction mixture was heated in an oil bath maintained at 90° for 8 h, cooled and the solid was removed by filtration. Removal of solvents gave **29** as a slight yellow oil (185 mg). MS (DCI, NH_3) $(M+NH_4)^+$ 466

The bisazide **29** was subjected to hydrogenation as usual over 25 mg of Pearlman's catalyst in 10 mL of ethyl acetae to give 172 mg of the diamine **30**. An analytical sample was obtained by chromatography over florisil(hexane, then ethyl acetate: hexane). ^{1}HNMR(CD_3OD, 250 MHz) δ 3.7 (dd, 2H, J=2,4 Hz), 2.7 (bs, 2H), 1.2-1.6 (m, 12 H), 1.4 (s, 6H), 0.85 (t, 6 H, J=7 Hz).

d) (5S,6R,7R,8S)-5,8-bis[benzyloxycarbonylaminovalinylamino]-6,7-(isopropylidenedioxy)-dodecane **31**

50 mg of the diamine was coupled using the mixed anhydride method with 100 mg of Cbz-Val , 65 μL of N-methylmorpholine and 53 μL of isobutylchloroformate in 2 mL THF, and 3 mL DMF. Flash chromatography(silica gel, ethyl acetate: hexane 1:2) gave 42 mg of the titled product. ^{1}HNMR ($CDCl_3$, 250 MHz) d 7.4-7.3 (s, 10 H), 6.1 (d, 2H, J= 7 Hz), 5.2 (d, 2 H, J= 7 Hz), 5.1 (two doublets, 4 H, J= 12 Hz), 4.0 (m, 4 H), 3.7 (s, 2

H), 2.2 (m, 2H), 1.2-1.6 (m, 12 H), 1.3 (s, 6 H), 1.0 (d, 6 H, J= 7 Hz), 0.9 (d, 6 H, J= 7 Hz), 0.8 (t, 6 H, J= 7 Hz).

e) (5S,6R,7R,8S)-5,8-bis[benzyloxycarbonylaminovalinylamino]-dodecane-6,7-diol <u>32</u>

25 mg of the acetonide was suspended in 2 mL of 70 % acetic acid and heated in an oil bath at 75° for 8 h. The reaction mixture was cooled and the solvents removed in vacuo. The residue was triturated with ether/hexane to give 20 mg of a colorless solid. MS(FAB) $(M+H)^+$ 699.5; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.5 (s, 10 H), 6.3 (d, 2H, J= 7 Hz), 5.2 (d, 2H, J=7 Hz), 3.8-4.0 (m, 4 H), 3.4 (s, 2 H), 2.2 (m, 2 H), 1.1-1.9 (m, 12 H), 1.0 (d, 6 H, J=7 Hz), 0.9 (d, 6 H, J= 7 Hz), 0.8 (t, 6 H, J= 7 Hz).

Example 9

Preparation of 4S,5R,6R,7S)-4,7-bis(benzyloxycarbonylaminovalinylamino)-5,6-dihydroxy-2,9-dimethyldecane 39.

a) (4R,5R,6R,7R)-4,7-dihydroxy-5,6-(isopropylidenedioxy)-2,9-dimethyldeca-2,9-diene <u>33</u>

A standard solution of isopropenyllithium was prepared by reacting 700 mg of lithium and 7 mL (75 mmol) of 2-bromopropene at 0° for 1h (in 75 mL of diethyl ether). ~16 mmol of this solution was added at -78° to a suspension of 1.5g (7.77 mmol) of copper(1) iodide and warmed to -45° over half hour. The dark brown mixture was recooled to -78° and a solution of 2.5 g (13.5 mmol) of the bisepoxide <u>C</u> in 50 mL of diethyl ether was added. The reaction mixture was stirred at -78° for 1 h and slowly warmed to room temperature. Quenched with saturated ammonium chloride and ammonium hydroxide, extracted with ether, washed with ammonium hydroxide, dried over anhydrous sodium sulfate and solvents removed in vacuo to give 3.20 g (88 %) of <u>33</u> a colorless oil. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 4.9 (s, 2H), 4.82 (s, 2 H), 3.7 (bs, 4H), 2.5 (d, 2 H, J= 13 Hz), 2.1 (m, 2 H), 1.8 (s, 6 H), 1.3 (s, 6 H).

b) (4R,5R,6R,7R)-4,7-dihydroxy-5,6-(isopropylidenedioxy)-2,9-dimethyldecane <u>34</u>

2.10 g (7.75 mmol) of the diol was dissolved in 10 mL of methylene chloride and mixed with 0.5 g of Crabtree catalyst. The reaction mixture was subjected to hydrogenation at 1 atm using a balloon filled with hydrogen. After stirring for 24 h the catalyst was precipitated out by the addition of ether, filtered through silica gel and washed with ether. Removal of solvents gave 1.95 g (93 %) of <u>34</u> as a colorless oil. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 3.8-3.5 (m, 4 H), 1.8 (m, 2 H), 1.6-1.4 (m, 4 H), 1.35 (s, 6 H), 0.9 (d, 6 H, J= 7 Hz), 0.85 (d, 6 H, J= 7 Hz).

c) (4R,5R,6R,7R)-4,7-bis(methanesulfonyloxy)-5,6-(isopropylidenedioxy)-2,9-dimethyldecane 35

To 1.88 g (6.87 mmol) of the diol 24 in 15 mL of pyridine was added at 0° 4 mL of methanesulfonyl chloride and stirred for 2h. The reaction mixture was warmed to room temperature and stirred overnight. Poured into 50 mL of ice-cold 3 N hydrochloric acid, extracted with methylene chloride, washed with 3 % sodium bicarbonate, dried over anhydrous sodium sulfate and solvents removed in vacuo to give a dark brown oil. Flash chromatography provided 1.65 g (55%) of the bis mesylate 35. MS (DCI, NH_3) $(M+NH_4)^+$ 448.3; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 4.85 (m, 2 H), 4.1 (bs, 2 H), 3.1 (s, 6 H), 1.4-2.0 (m, 6 H), 1.4 (s, 6 H), 1.0 (d, 6 H, J= 7 Hz), 0.9 (d, 6 H, J= 7 Hz).

d) (4S,5R,6R,7S)-4,7-bis(azido)-5,6-(isopropylidenedioxy)-2,9-dimethyldecane 36 and (4S,5R,6R,7S,)-4,7-bis(amino-5,6-(isopropylidenedioxy)-2,9-dimethyldecane 37

To a solution of 1.19 g of the bismesylate 35 in 10 mL of DMSO was added 1.1 g (17 mmol) of sodium azide and heated to 100° in an oil bath for 10 h. The reaction mixture was cooled, sodium azide was removed by filtration, washed wih ether and combined solvents removed in vacuo. The combined organic extracts were diluted with ether, washed with 50 mL of water, dried over anhydrous sodium sulfate and solvents removed in vacuo to give 810 mg of the bis azide 36, which was taken directly for the reduction without further purification.

790 mg of the crude azide obtained above was subjected to hydrogenation over 400 mg of Pearlman's catalyst at 1 atm hydrogen. Stirred overnight, catalyst was filtered through florisil washed with 75 mL of ether and solvents removed in vacuo. The residual oil was chromatographed over 10 g florisil (hexane, then ethyl acetate: hexane 1:4 and finally methanol) to provide 620 mg of the diamine 37 as a colorless oil. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 3.7 (q, 2 H, J= 4 Hz), 2.75 (m, 4 H), 1.75 (m, 2 H), 1.4 (s, 6 H), 1-1.3 (m, 6 H), 0.9 (d, 6 H, J= 7 Hz), 0.8 (d, 6 H, J= 7 Hz).

e) 4S,5R,6R,7S)-4,7-bis(benzyloxycarbonylaminovalinylamino)-5,6-(isopropylidene-dioxy)-2,9-dimethyldecane 38

To 200 mg (0.8 mmol) of Cbz-Val in 5 mL of THF at -40° was added 130 µL of N-methylmorpholine followed by 106 µL (0.8 mmol) of isobutylchloroformate. The reaction mixture was stirred for 30 min and added a solution of 75 mg (0.276 mmol) of diamine 37 in 5 mL of THF. Stirred at -40° for 2 h, warmed to room temperature and stirred for 16 h. Diluted with 100 mL of ethyl acetate washed with 2x50 mL of 5 % hydrochloric acid, 2x50 mL of 5 % sodium bicarbonate, dried over anhydrous magnesium sulfate and solvents removed in vacu to give 300 mg of a crude product which on trituration with 20 mL of hexane and 4 mL of ether gave 190 mg of 38 as a colorless solid.

MS (ESMS) $(M-H)^+$ 737.2; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.3 (s, 10 H), 5.8 (bd, 2 H, J= 7 Hz), 5.1 (d, 2 H, J= 7 Hz), 5.0 (bs, 4 H), 4.1 (m, 2 H), 3.9 (dd, 2 H, J= 7, 9 Hz), 2.2 (m, 2 H), 1.1-1.6 (m, 6 H), 1.2 (s, 6 H), 0.9 (d, 6 H, J= 7 Hz), 0.75 (two overlapping doublets, 12H, J= 7 Hz).

f) (4S,5R,6R,7S)-4,7-bis(benzyloxycarbonylaminovalinylamino)-5,6-dihydroxy 2,9-dimethyldecane 39

45 mg of the coupled product 38 was suspended in 5 mL of 70 % acetic acid and heated in an oil bath maintained at 85° for 10 h. The reaction mixture was cooled and solvents removed in vacuo to give a white solid. Anal Calcd for $C_{38}H_{58}N_4O_8$.1/2 H_2O C(64.47), H (8.40), N (7.91): Found C(64.36), H98.39), N(7.82); MS(ESMS) $(M+H)^+$ 699.2: $(M+Na)^+$ 721.2; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.35 (s, 10 H), 6.25 (d, 2 H, J= 7 Hz), 5.2 (d, 2 H, J= 7 Hz), 5.0 (s, 4 H), 4.0 (m, 2 H), 3.9 (dd, 2 H, J= 7, 9 Hz), 3.35 (s, 2 H), 2.2 (m, 2 H), 1.1-1.6 (m, 6 H), 1.0 (d, 6 H, J= 7 Hz), 0.9 (d, 6 H, J= 7Hz), 0.85 (b, 12 H).

Example 10

Preparation of (4S,5R,6R,7S)-4,7-bis(benzyloxycarbonylaminoalanylamino)-5,6-dihydroxy-2,9-dimethyldecane 41.

a) (4S,5R,6R,7S)-4,7-bis(benzyloxycarbonylaminoalanylamino)-5,6-(isopropylidene-dioxy)-2,9-dimethyldecane 40

A mixture of 51 mg (0.1875 mmol) of the diamine, 109.3 mg (0.4125 mmol) of AlaCbz, 85 mg (0.4125 mmol) of DCC and 68 mg (0.5 mmol) of HOBT was stirred overnight. The precipitated dicyclohexylurea was removed by filtration and solvents removed in vacuo to give 72 mg of 40 as a colorless solid. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.3 (s, 10 H), 6.1 (d, 2 H, J= 7 Hz), 5.3 (d, 2 H, J= 7 Hz), 5.1 (m, 4 H), 4.1 (m, 4 H), 3.5 (s, 2 H), 1.2-1.1.6 (m, 6 H), 1.4 (d, 6 H, J= 7 Hz), 1.2 (s, 6 H), 0.8 (two overlapping doublets, 12 H, J= 7 Hz).

b) (4S,5R,6R,7S)-4,7-bis(benzyloxycarbonylaminoalanylamino)-5,6-dihydroxy2,9-dimethyldecane 41

10 mg of the coupled product 40 was suspended in 2 mL of 70 % acetic acid and heated in an oil bath at 80° for 10 h. the reaction mixture was cooled and solvents removed in vacuo and the residue on trituration with hexane/ether provided 8 mg of the titled compound 41. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.3 (s, 10 H), 6.3 (ds, 2 H), 5.3 (bs, 2 H), 5.1 (bs, 4 H), 4.1 (m, 4 H), 3.4 (bs, 2H), 1.5(m, 6 H), 1.3 (d, 6 H, J= 7 Hz), 0.8 (bs, 12 H).

Example 11

Preparation of (2S,3R,4R,5S)-dibenzyloxy-2,5-bis(carboxybenzyloxyvalinyl)amino-3,4-hexandiol 47.

a) 1,6-dibenzyloxy-3,4-O-isopropylidene-D-mannitol 42

Sodium hydride (~50% oil dispersion) (1.2 g, ca. 25 mmol) was washed with dry THF (2 x 10 mL), relayered with THF (20 mL), cooled to 4°C and anhydrous benzyl alcohol (5.2 mL, ca. 50 mmol) was added dropwise. To the resulting solution at 4° C was added to a solution of 1,2:5,6-dianhydro-3,4-O-isopropylidene-D-mannitol C in THF (2 mL). The cooling bath was removed and the reaction was stirred at 23° C for 18 h, poured into 1N HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The extract was washed with H_2O (50 mL), and satd. aq. NaCl (50 mL), dried (Na_2SO_4), concentrated and flash chromatographed with hexane/EtOAc to give 3.0 g (75%) of the titled compound 42. ^1H ($CDCl_3$) 7.3 - 7.2 (m,10), 4.54 (dd, 4), 3.96 (m,2), 3.87 (m, 2), 3.75 (m, 4), 3.54 (dd, 2), 1.32 (s, 6).

b) 1,6-dibenzyloxy-2,5-ditosyl-3,4,O-isopropyidene-D-mannitol 43

1,6-Dibenzyloxy-3,4-O-isopropylidene-D-mannitol 42 (402 mg, 1.0 mmol), tosyl chloride (764 mg, 4.0 mmol) and pyridine (10 mL) were stirred for 3 days, poured into ice cold 3N HCl (30 mL) and extracted with EtOAc (3 x 25 mL). The extracts were washed with 3N HCl (3 x 25 mL), 5% $NaHCO_3$ (25 mL), and satd. aq. NaCl (5 mL), dried (Na_2SO_4), concentrated and flash chromatographed with hexane/EtOAc to give 550 mg (77%) of the titled compound 43. ^1H ($CDCl_3$) 7.66(m, 4), 7.40 - 7.15 (m, 16), 4.83 (m, 2), 4.37 (m,6), 3.82 - 3.60 (m, 4), 2.37 (s, 6), 1.34 (s,6).

c) (2S,3R,4R,5S)-dibenzyloxy-2,5-diazido-3,4-O-isopropylidene hexandiol 44

Compound 43 (1.00 g, 1.41 mmol), DMF (20 mL) and NaN_3 (0.917 g, 14.1 mmol) were combined and heated to 85°C for 24 h, filtered and the insoluble NaN_3 was washed with DMF and the filtrate was concentrated in vacuo. The residue was combined with H_2O (30 mL) and extracted with EtOAc (3 x 50 mL). The extract was washed with H_2O (2 x 25 mL), satd. aq. NaCl (25 mL), dried (Na_2SO_4)and flash chromatographed in hexane/EtOAc to give 0.465 g (73%) of the titled compound 44. ^1H ($CDCl_3$) 7.33(m, 10), 4.66 (dd, 4), 4.18 (m, 2), 3.87 - 3.68 (m, 4), 3.46(m, 2), 1.44 (s, 6).

d) (2S,3R,4R,5S)-dibenzyloxy-2,5-diamino-3,4-O-isopropylidene hexandiol <u>45</u>

A solution of <u>44</u> (203 mg, 0.45 mmol) in THF (1 mL) was added to a 1 M solution of LAH in THF (4.5 mL, 4.5 mmoL). The reaction was stirred at 23°C for 15 min and then the excess LAH was quenched by the slow addition of EtOAc (2 mL) and then 10% NaOH (20 mL). Extraction with EtOAc (3 x 50 mL) and washing the extract with satd. aq. NaCl (10 mL), drying (Na_2SO_4), concentration and flash chromatography over Florisil (CH_2Cl_2/CH_3OH) gave 0.146 g (81%) of the titled compound <u>45</u>. ^1H ($CDCl_3$) 7.32 (m, 10), 4.51 (s, 4), 4.07 (s, 2), 3.50 (m,2), 3.43 (m, 2), 2.94 (m, 2), 1.65 (br m, 4), 1.39 (s, 6).

e) (2S,3R,4R,5S)-dibenzyloxy-2,5-bis(carboxybenzyloxyvalinyl)amino-3,4-O-isopropylidene hexandiol <u>46</u>

Cbz-Valine (166 mg, 0.66 mmol) and THF (3 mL) were cooled to -15°C and NMM (72 uL, 0.66mmol) was added followed by i-BuOCOCl (94 uL, 0.73 mmol). The resulting mixture was stirred for 1 min and then diol <u>45</u> (120 mg, 0.3 mmol) in THF (1 mL) was added. The mixture was warmed to 23°C, stirred for 16 h, diluted with THF (5 mL) and filtered. The insoluble NMM·HCl was washed with more THF and the filtrate was concentrated, redissolved in EtOAc (50 mL), washed with H_2O (10 mL) and satd aq. NaCl (10 mL), dried (Na_2SO_4), concentrated and flash chromatographed with CH_2Cl_2/CH_3OH to elute the expected product as a solid and an oil. Trituration with Et_2O and filtration gave 0.121 g (47%) of a pure solid <u>46</u>. ^1H ($CDCl_3$) 7.32 (m, 20), 4.48 (m,6), 4.00 (m, 2), 3.52 (m,4), 2.10 (m,2), 1.93 (m, 2), 1.32 (m, 6), 0.92 (d, 6), 0.85 (d, 6).

f) (2S,3R,4R,5S)-Dibenzyloxy-2,5-bis(carboxybenzyloxyvalinyl)amino-3,4-hexandiol <u>47</u>

(2S,3R,4R,5S)-dibenzyloxy-2,5-bis(carboxybenzyloxyvalinyl)amino-3,4-O-isopropylidene hexandiol <u>46</u> (121 mg, 0.14 mmoL) was combined with 70% acetic acid (12 mL) and heated to 90°C for 14 h, cooled and concentrated in vacuo. The residue was dissolved in EtOAc (50 mL) and washed with 5% $NaHCO_3$ (2 x 20 mL), H_2O (20 mL), and satd. aq. NaCl (20 mL), dried (Na_2SO_4), concentrated and flash chromatographed with CH_2Cl_2/CH_3OH to elute 39 mg (34%) of (2S,3R,4R,5S)-Dibenzyloxy-2,5-bis(carboxybenzyloxyvalinyl)amino-3,4-hexandiol <u>47</u>. mp(methanol): 223°C: Anal. Calcd. for $C_{46}H_{58}N_4O_{10}\cdot 1/2\ H_2O$: C, 66.09; H,7.11; N, 6.70. Found: C, 66.23; H, 6.93; N, 6.68.; ^1H ($CDCl_3$) δ 7.32 (m, 20), 5.07 (m,4), 4.48 (m,4), 4.35 (m, 2), 4.06 (m, 2), 3.63 (m, 4), 2.10 (m, 4), 0.91 (d, 6), 0.85 (d, 6); MS (FAB): [M+H$^+$] 827.3.

ENZYME INHIBITION

Inhibition of HIV protease activity

The inhibition assay has been previously described in Dreyer et al. Proc. Natl. Acad. Sci. USA, 86, 9752-9756 (1989) and Moore et al. Bioch. Bioph. Res. Com., 159, 420 (1989). A typical assay contained 10 mL MENDT buffer (50 mM Mes (pH 6.0; 2-(N-morpholino) ethanesulfonic acid), 1 mM EDTA, 1mM dithiothreitol, 200 mM NaCl, 0.1% Triton X-100); 2, 3, or 6 mM N-acetyl-L-arginyl-L-alanyl-L-seryl-L-glutaminyl-L-asparaginyl-L-tyrosyl-L-prolyl-L-valyl-L-valinamide (Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH_2; K_m = 7 mM); and micromolar and submicromolar concentrations of synthetic compounds. Following incubation at 37°C for several minutes, the reaction was initiated with 0.001-0.10mg purified HIV protease. Reaction mixtures (37°C) were quenched after 10-20 minutes with an equal volume of cold 0.6 N trichloroacetic acid, and, following centrifugation to remove precipitated material, peptidolysis products were analyzed by reverse phase HPLC (Beckman Ultrasphere ODS, 4.5 mm x 25 mm; mobile phase; 5-20% acetonitrile/H_2O - .1% TFA 915 min.), 20% acetonitrile/H_2O - .1% TFA (5 min) at 1.5 mL/min, detection at 220 nm. The elution positions of Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH2 (17-18 min) and Ac-Arg-Ala-Ser-Gln-Asn-Tyr (10-11 min) were confirmed with authentic material. Initial rates of Ac-Arg-Ala-Ser-Gln-Asn-Tyr formation were determined from integration of these peaks, and typically, the inhibitory properties of the synthetic compounds were determined from slope/intercept analysis of a plot of 1/v vs. [inhibitor] (Dixon analysis). K_i values resulting from this type of primary analysis are accurate for competitive inhibitors only, and under conditions in which the Michaelis constant of the substrate used is well-determined.

It is desirable for the compounds of this invention to have Ki values less than 50μM, preferably less than 10μM and more preferably less than 1μM.

Inhibition of rHIV-1 Protease

Compound	Ki(μM)
2	5.8
5	39.
9	0.58
10	0.80
11	2.4

ENZYME INHIBITION

Inhibition of HIV protease activity

The inhibition assay has been previously described in Dreyer et al. Proc. Natl. Acad. Sci. USA, 86, 9752-9756 (1989) and Moore et al. Bioch. Bioph. Res. Com., 159, 420 (1989). A typical assay contained 10 mL MENDT buffer (50 mM Mes (pH 6.0; 2-(N-morpholino) ethanesulfonic acid), 1 mM EDTA, 1mM dithiothreitol, 200 mM NaCl, 0.1% Triton X-100); 2, 3, or 6 mM N-acetyl-L-arginyl-L-alanyl-L-seryl-L-glutaminyl-L-asparaginyl-L-tyrosyl-L-prolyl-L-valyl-L-valinamide (Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH_2; K_m = 7 mM); and micromolar and submicromolar concentrations of synthetic compounds. Following incubation at 37°C for several minutes, the reaction was initiated with 0.001-0.10mg purified HIV protease. Reaction mixtures (37°C) were quenched after 10-20 minutes with an equal volume of cold 0.6 N trichloroacetic acid, and, following centrifugation to remove precipitated material, peptidolysis products were analyzed by reverse phase HPLC (Beckman Ultrasphere ODS, 4.5 mm x 25 mm; mobile phase; 5-20% acetonitrile/H_2O - .1% TFA 915 min.), 20% acetonitrile/H_2O - .1% TFA (5 min) at 1.5 mL/min, detection at 220 nm. The elution positions of Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH2 (17-18 min) and Ac-Arg-Ala-Ser-Gln-Asn-Tyr (10-11 min) were confirmed with authentic material. Initial rates of Ac-Arg-Ala-Ser-Gln-Asn-Tyr formation were determined from integration of these peaks, and typically, the inhibitory properties of the synthetic compounds were determined from slope/intercept analysis of a plot of 1/v vs. [inhibitor] (Dixon analysis). K_i values resulting from this type of primary analysis are accurate for competitive inhibitors only, and under conditions in which the Michaelis constant of the substrate used is well-determined.

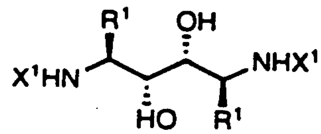
It is desirable for the compounds of this invention to have Ki values less than 50μM, preferably less than 10μM and more preferably less than 1μM.

Inhibition of rHIV-1 Protease

Compound	Ki(μM)
2	5.8
5	39.
9	0.58
10	0.80
11	2.4

Following the procedures set forth herein and the teachings of the foregoing examples the compounds set forth in the following Table can be prepared having the structure and the substituent groups as designated therein.

TABLE OF COMPOUNDS



(I)

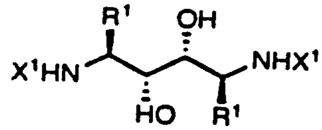
No.	X^1	R^1
2	Cbz-AlaAla	ethyl
5	AlaAla	ethyl
9	Cbz-AlaAla	i-Bu
10	AlaAla	i-Bu
11	Cbz-Ala	i-Bu
101	Cbz-Val	i-Bu
102	β-Ala	i-Bu
103	β-AlaVal	i-Bu
104	H	i-Bu
105	BocAla	I-Bu
106	AcAlaAsn	i-Bu
107	AcGlnAsn	i-Bu
108	Cbz-PheAla	i-Bu
109	trifluoroAlaAla	i-Bu
110	Cbz-trifluoroAlaAla	i-Bu
111	trifluoroAla	i-Bu
112	Cbz-trifluoroAla	i-Bu
113	$Ph(CH_2)_2CO$	i-Bu
114	Boc	i-Bu
115	Cbz-	i-Bu
116	Ac	i-Bu
117	$PhSO_2$	i-Bu
118	HCO	i-Bu
119	Propionyl	i-Bu
120	i-Butyryl	i-Bu
121	$Ph(CH_2)_2CO$	i-Bu
122	$PhSO_2$Val	i-Bu

123	Phenyllactoyl	i-Bu
124	Phenyllactoyl-Val	i-Bu
125	Cbz-Ala	$PhCH_2$
126	AlaAla	$PhCH_2$
127	Cbz-Val	i-Butenyl
128	Cbz-Val	2-Propenyl
129	Cbz-Val	3-Butenyl
130	Cbz-Val	n-Pentyl
131	Cbz-Val	$Ph(CH_2)_2$-
132	Cbz-Val	Cyclohexyl-CH_2-
133	Cbz-Val	2-Napthyl-CH_2-
134	Cbz-Val	3-Napthyl-CH_2-
135	Cbz-Val	2-Butynyl
136	Cbz-Val	3-Indoylmethyl
137	Cbz-Val	trans-3-phenyl-3-propenyl
138	H	ethyl
139	Cbz-Val	N-Piperidinyl-CH_2-
140	Cbz-Val	N-Morpholinyl-CH_2-
141	Cbz-Val	$(CH_3)_2N$-CH_2
142	Cbz-Val	t-ButylNH-CH_2-
143	Cbz-Val	N-Imidazoyl-CH_2
144	Cbz-Val	PhCONH-CH_2
145	Cbz-Val	N-Indoyl-CH_2
146	Cbz-Val	t-ButylCONH-CH_2
147	Cbz-Val	$BocNHCH_2$
148	Cbz-Val	NH_2CH_2
149	Cbz-Val	N-benzimidazolyl
150	Cbz-Val	$PhCH_2O$-CH_2
151	Cbz-Val	PhO-CH_2
152	Cbz-Val	$CH_3(CH_2)_2O$-CH_2
153	Cbz-Val	CH_3O-CH_2
154	Cbz-Val	$(CH_3)_2CHO$-CH_2
155	Cbz-Val	t-Butyl-O-CH_2
156	Cbz-Val	$(CH_3)_2CHCH_2O$-CH_2
157	Cbz-Val	$CH_3CH_2(CH_3)CHO$-CH_2
158	Cbz-Val	Cyclohexyl-O-CH_2
159	Cbz-Val	$PhCH_2OCH_2O$-CH_2
160	Cbz-Val	CH_3OCH_2O-CH_2

161	Cbz-Val	$CH_3OCH_2CH_2OCH_2OCH_2$
162	Cbz-Val	CH_3S-CH_2
163	Cbz-Val	$PhS-CH_2$
164	Cbz-Val	$(CH_3)_2CHS-CH_2$
165	Cbz-Val	$CH_3(CH_2)_2S-CH_2$
166	Cbz-Val	$CH_3(CH_2)_3S-CH_2$
167	Cbz-Val	$CH_3S(O)-CH_2$
168	Cbz-Val	$CH_3S(O)_2-CH_2$
169	Cbz-Val	$PhS(O)_2-CH_2$
170	Cbz-Val	i-Propyl-$S(O)_2-CH_2$
171	Cbz-Val	n-Propyl-$S(O)_2-CH_2$
172	Cbz-Val	n-Butyl-$S(O)_2-CH_2$
173	Cbz-Val	$(Ph_2O)_2P(O)-CH_2$
174	Cbz-Val	$(CH_3O)_2P(O)-CH_2$
175	Cbz-Val	(n-ButylO)$_2P(O)-CH_2$
176	Cbz-Val	$(EtO)_2P(O)-CH_2$
177	Cbz-Ala	$(CH_3O)_2P(O)-CH_2$

CLAIMS:

1. A compound having the structure:



wherein X^1 is $A-(B)_n-$ where n = 0-2; and

B is, independently, an α-amino acid chosen from the group:- Ala, Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr, Tyr, Val, His, or trifluoroalanine, wherein the amino group of B is bonded to A or the carboxy group of the adjacent residue B, whichever is appropriate, and the carboxy group of B is bonded to the amino group of the adjacent residue B or the structure, whichever is appropriate; and

A is covalently attached to the amine group of the adjacent residue B or to the amine group of the structure if n=0, and is:

1) trityl,

2) hydrogen,

3) C_1-C_6 alkyl,

4) R^3-CO- wherein R^3 is:

a) hydrogen,

b) C_1-C_6 alkyl, unsubstituted or substituted with one or more hydroxyl groups, chlorine atoms, or fluorine atoms,

c) phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4, wherein R^4 is:

i) C_1-C_4 alkyl,

ii) halogen, where halogen is F, Cl, Br or I,

iii) hydroxyl,

iv) nitro,

v) C_1-C_3 alkoxy, or

vi) $-CO-N(R^{10})_2$ wherein R^{10} is, independently, H or C_1-C_4 alkyl; or

d) a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;

5) phthaloyl wherein the aromatic ring is unsubstituted or substituted with one or more substituents R^4;

6) $R^5(R^6R^7C)m$-CO- wherein m = 1-3 and R^5, R^6, and R^7 are independently:

a) hydrogen,

b) chlorine or fluorine,

c) C_1-C_3 alkyl unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups,

d) hydroxyl,

e) phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4,

f) C_1 - C_3 alkoxy,

g) a 5-7 member heterocycle, or

h) R^5, R^6, and R^7 may be independently joined to form a monocyclic, bicyclic, or tricycle ring system each ring of which is C_3-C_6 cycloalkyl;

7) $R^5(R^6R^7C)m$ W- wherein m = 1-3 and W is OCO or SO_2 and R^5, R^6, and R^7 are as defined above, except R^5, R^6, and R^7 are not chlorine, fluorine or hydroxyl if they are adjacent to W;

8) R8-W- wherein R^8 is a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;

9) R^9-W- wherein R^9 is phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4;

10) R^5-(R^6R^7C)m-P(O)(OR^{11})- wherein R^{11} is C_1 - C_4 alkyl or phenyl;

11) R^8-P(O)(OR^{11})-; or

12) R^9-P(O)(OR^{11})-;

R^1 is:

1) -CH_2R^{12} wherein R^{12} is

a) NH-A wherein A is defined as above;

b) R^5-(R^6R^7C)m-;

c) R^5-(R^6R^7C)m V- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-(R^6R^7C)m-S(O)n- wherein m = 1-3 and n = 0-2 and R^5, R^6 and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-S(O)n-,

f) R^9-S(O)n-,

g) (R^{13}O)P(O)(OR^{14})- wherein R^{13} and R^{14} are, independently:

i) C_1-C_6 alkyl,

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) R^{13}P(O)(OR^{14})-,

i) $N(R^{10})_2$.

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

2) hydrogen,

3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

4) C_3-C_7 cycloalkyl;

and pharmaceutically acceptable salts thereof.

2. A compound as defined in claim 1 wherein R^1 is C_1-C_6 alkyl, benzyloxymethyl, 3-phenylpropyl or benzyloxy.

3. A compound as defined in claim 2 wherein X^1 is CbzAla, AlaAla, Val, CbzVal, Cbz or hydrogen.

4. A compound as defined in claim 1 wherein R^1 is benzyloxymethyl.

5. A compound as defined in claim 1 wherein R^1 is 3-phenylpropyl.

6. A compound of claim 1 wherein the protease activity inhibition constant is less than about 10 µM.

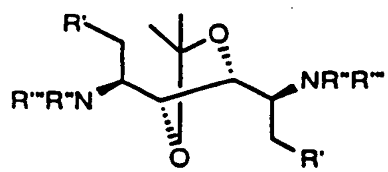
7. A compound according to claim 1 for use in a medicament.

8. A pharmaceutical composition comprising a compound according to claim 1 and a pharmacetically acceptable carrier.

9. A method of treating infection by a retrovirus which comprises administering a compound according to claim 1.

10. A method according to claim 9 wherein the retrovirus is the Human Immunodeficiency Virus type 1.

11. A process for preparing a compound of the formula:



wherein R' is

1) a) NH-A wherein A is defined in claim 1;

b) R^5-$(R^6R^7C)_m$-;

c) R^5-$(R^6R^7C)_m$ V- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-$(R^6R^7C)_m$-S- wherein m = 1-3 and R^5, R^6 and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-S-,

f) R^9-S-,

g) $(R^{13}O)P(O)(OR^{14})$- wherein R^{13} and R^{14} are, independently:

i) C_1-C_6 alkyl,

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) $R^{13}P(O)(OR^{14})$-,

i) $N(R^{10})_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

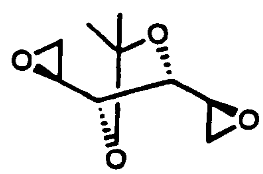
2) hydrogen,

3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

4) C_3-C_7 cycloalkyl, and

R" and R"' are hydrogen, an amino-protecting group or taken together are N_2, which comprises

1) reacting a compound of the formula:

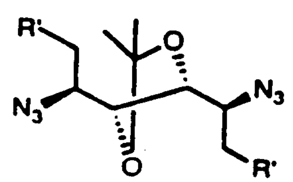


with a compound R'-Z, wherein Z is a moiety which renders R' nucleophilic,

2) converting the resulting hydroxy groups to displaceable groups,

3) reacting the displaceable groups with a nitrogen nucleophile.

12. A compound of the formula:



wherein:

R' is: 1) a) NH-A wherein A and R^5-R^{10} are defined as in claim 1;

b) R^5-$(R^6R^7C)m$-;

c) R^5-$(R^6R^7C)m$ V- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-$(R^6R^7C)m$-S(O)n- wherein m = 1-3 and n = 0-2 and R^5, R^6 and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-S(O)n-,

f) R^9-S(O)n-,

g) $(R^{13}O)P(O)(OR^{14})$- wherein R^{13} and R^{14} are, independently:

i) C_1-C_6 alkyl,

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) $R^{13}P(O)(OR^{14})$-,

i) $N(R^{10})_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH_2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

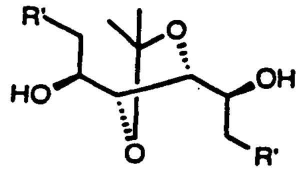
p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

2) hydrogen,

3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

4) C_3-C_7 cycloalkyl.

13. A compound of the formula:



wherein R' is as defined in claim 12.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/04756

I. CLASSIFICATI[illegible] [illegible]T MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C[illegible] 21[illegible]/00, 215/00, 233/00, 261/00

US CL : 560/25,158; 564/153,155,157,158,159,346,360,507

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	560/25,158; 564/153,155,157,158,159,346,360,507

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [*]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No [13]
A	US, E, RE 29,903 (KIRBY) 06 FEBRUARY 1979 See example 7.	3
A	US, A, 3,855,297 (DIANA) 17 DECEMBER 1974 See examples.	3
A	US, A, 3,987,029 (KIRBY) 19 OCTOBER 1976 See example 7.	3
X	US, A, 4,237,273 (HORVATH) 02 DECEMBER 1980 See example 2.	3

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 OCTOBER 1991	07 NOV 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	MICHAEL SHIPPEN

Form PCT/ISA/210 (second sheet) (Rev.11-87)